Human Genome Modification

An Honors Thesis (HONR 499)

by

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Abstract

The innovative technology of human genome editing is rapidly developing. In this thesis, I will first discuss the history behind genetic modification. I will then go over the advantages and drawbacks of human gene editing. Finally, I will support the importance of regulation and offer possible benefits of worldwide harmonization of regulatory standards.

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Process Analysis

The thesis you are about to read is the product of years of hard work and effort. I was faced with numerous challenges along the way and was able to overcome them. Consequently, I gained invaluable insights about myself and the way that I learn. Additionally, writing this thesis provided me with the opportunity to put my academic knowledge and personal judgment to use. Completing this thesis proved to be very difficult, but equally rewarding.

The process of my research for writing my thesis was quite long. I started doing research for it at the end of my freshman year at Ball State. My topic has changed and evolved overtime, but I knew from the beginning that I wanted to research an ethically controversial topic. During the beginning stages of my research, I was taking various honors courses that involved topics such as religion, ethics, science, and society. I was very interested in how all of these topics were interrelated, and I had played with the idea of writing my thesis about how the advancement of science has affected society, and more specifically, religious culture. As I continued in my biology and pre-med coursework, I became much more interested in the societal effects of science. Many of my honors courses were discussion based and philosophy driven, contributing to my continued interest in ethics.

In the Spring of my junior year, I took an introductory genetics course that would prove to be very significant in the further development of my honors thesis topic. Throughout this course I found myself being constantly amazed by the scientific concepts of genetics. I was also uncharacteristically inquisitive about the future of genetics and the implications of the research being done all around the world. Following the introductory course in genetics, I opted to take

an elective course that was more focused on the genetics of humans, and more specifically, the problems with our genome. Throughout this course not only did I learn more about human genetics, but I also developed crucial research skills and became efficient in finding and understanding scholarly and scientific articles.

My love for genetics had grown so much that I even contemplated changing my career to become a genetic counselor instead of a medical doctor. While I did not follow through with this change, I knew that I had found the topic of my honors thesis. The passion and interest I have in genetics made writing my thesis very rewarding and surprisingly fun.

Originally, I was going to request that my thesis advisor be my genetics professor. She happily agreed to take on that role, but as I started working with her, I realized that my vision for my thesis was quite different from hers. I wanted to take a more philosophical approach to the topic rather than a research data analysis approach. Realizing this, I sought out another advisor with a stronger background in philosophy. During my search, I was presented with the opportunity to work on my thesis in a classroom setting under the advisement of a honors professor, who happened to teach humanities courses. This class was exactly what I needed, as it not only provided a structured schedule for me to work on my thesis, but also provided a panel of peers to bounce ideas off of and formulate new ideas with. Ecstatic, I hopped on this opportunity right away and was chosen to join the class.

When the class began, I knew that I had made the right decision. My professor, Jason Powell, and classmates were immensely helpful in giving my thesis the kickstart it needed. With

Jason's guidance, I was able to break the long research and writing process up into bite-size pieces that didn't seem so frightening.

The idea of the honors thesis was previously very intimidating and I found myself seriously considering dropping out of the Honors College to avoid having to buckle down and write my thesis. To have taken all of the honors course work throughout my four years at Ball State just to drop out at the last minute would have been ridiculous, and I knew that. But to tackle the longest research essay I would ever write up to this point, on top of all of my other senior coursework, also seemed impossible. The thesis class provided me with the structure and confidence that I needed to accomplish such a daunting task.

There were multiple challenges that I faced while researching and writing my thesis. The first challenge I had to overcome was figuring out how to narrow down my topic. Originally, I was afraid that if my topic was too narrow, that I wouldn't have enough to write about. However, I found that my original topic, "Ethics of Genetic Modification in Humans," was far too broad and organization attempts were a nightmare. There was simply too much to say and too many directions I could go with it. I also felt that by choosing this topic, I would have to come to a conclusion as to whether I agreed with modifying the human genome or not.

This brings me to my next major challenge of deciding exactly what my views were on the topic. I did tons of research and read multiple different views on the ethics of human genome modification and found both the pros and cons very compelling. The future medical doctor in me loved the idea of a possible cure to devastating genetic diseases, the biologist in me loved the scientific progress being made, but the realist in me understood that there were

many ways that such a powerful and unpredictable technology could go awry. For these reasons, I felt that I couldn't decide whether I fully supported this technology or not. At first this challenge was very hard to overcome and it definitely slowed my progress. However, after multiple discussions with peers, family, and Jason, I was able to find a way around this obstacle. I realized that this was my thesis and I did not have to make any decisions I didn't feel comfortable with. I also decided that ultimately, the question of whether or not I agreed with the practice was not really relevant.

Extensive research and experimentation focused on developing the technology to alter the human genome are already underway. To me, this means that enough people must agree with the importance of the technology for us to be spending billions of dollars in research labs all around the world. Therefore, I concluded that the question we should be asking is no longer whether we agree with the technology or not, but instead, how we will regulate its use. With this realization, I was able to both narrow down my topic and circumvent the obstacle of picking a side.

While those were the largest challenges I faced, they were certainly not the last. I found that choosing such an innovative and current issue for the topic of my thesis made the research process quite tedious. Sources are quick to become outdated and irrelevant with a technology that is developing and evolving so rapidly. I had to be careful about which sources I used and tried to keep the information as current as I could. This was quite difficult when sources that were not even 2 years old and less than a year apart had conflicting information. There were numerous times were I basically had to go back and restructure a whole argument due to

finding a more current, and therefore credible, source. While this was often aggravating, it was necessary for creating an accurate end-product.

The final major challenge I faced was finding a way to structure it in a unique but comprehensible way. Many of the sources I found had very logical structures that complimented their overall idea very well. Since the idea I wanted to get across was somewhat unique, I had to come up with a new way of structuring my thesis. After many rough drafts, I finally came up with an outline that I felt would effectively convey my thoughts in a comprehensible manner.

The challenges that presented themselves while I was completing my thesis were quite difficult to overcome. However, in retrospect, I am glad that I was given the opportunity to rise to the challenge. I was able to learn more about myself and my style of learning in the process. For example, I learned that I work much better when I have a plan of execution. When I attempted to just jump in and start writing, I essentially fell flat on my face. I became overstressed and continuously procrastinated, which only added to the stress. When I finally made myself sit down and crank out an outline, the work instantly became much more manageable and a noticeable stress load was lifted from my shoulders. I have already put this new insight to use in other areas of my life including my undergraduate coursework, medical school applications, and current job.

Completing this thesis was a huge accomplishment for me, one that I was very unsure of just a few months ago. As I mentioned before, I was so unsure that I seriously considered dropping out of the Honors College because of it. I know for a fact that I would have regretted

this decision down the road. I completed all of the other coursework successfully and if I had let the thesis be the reason I didn't graduate with honors, I would have been very disappointed in myself. To me, completing this thesis means that I can overcome even the most daunting challenges if I put my mind to it.

In conclusion, while the process of completing my thesis was a challenging one, it was also very rewarding. I find personal pride in the fact that rather than letting the fear of failure hold me back, I was able to push through and create a thesis I could be satisfied with. I contribute a large part of my success to being a part of Jason Powell's thesis class, as it provided me with the structure and support that independent work lacked. The personal insights I gained along the way were invaluable and will continue to be useful as I move forward in life.

Human Genome Modification

There have been countless debates regarding the use of genome editing technologies to alter the human germline. In general, people tend to fall into one of three main categories of the debate. The first being that we should not be tinkering with the human genome at all, often for fear that it will have apocalyptic-type consequences. The second popular stance is that the technology should only be used for the treatment of diseases that have no other cure. The third category encompasses those who hold some variation of the belief, "If we can, we should." While each side of the debate has good points, I would argue that the debate itself is no longer relevant.

There are obvious advantages to genetic modification in humans, but also many possible negative consequences. While some people push for progress, others do not believe it is worth the risk. Opinions aside, extensive research and technological advancements allowing for human genome modification are already underway. Therefore, I believe that the debate is no longer "if" we should genetically modify humans, but instead, how will we regulate it. My argument is that the best way to cultivate the benefits, while reducing the drawbacks, is to establish world-wide regulations to govern human genome modifications.

What is Genetic Modification?

Genetic modification, or genetic engineering, is the process of changing the DNA in an organism's genome. There are many ways of changing the DNA, including deleting sections of DNA, changing single or multiple base pairs, or inserting an additional copy of a gene. These

changes result in the cell's expression of a different phenotype. According to The American Heritage Science Dictionary phenotype is the expression of a specific trait, such as stature or blood type, based on genetic and environmental influences. Genetic engineering can be applied to any organism, from a virus to an elephant. Genetic modification is used in many areas of science including medicine, agriculture, technology, and scientific research.

History

Believe it or not, we have been using forms of genetic modification for over 30,000 years. While ancient technology was obviously not as advanced as it is now, since they had no concept of genetics, they were still able to influence the DNA of many organisms. The process used in ancient times is was later termed "artificial selection" or "selective breeding." These terms refer to the process of picking out desirable traits in an organism and breeding it with another organism with the same desirable traits, in order to combine and propagate the desired traits in the offspring.

Historians theorize that the first organism on which our ancestors used this process was what we now call dogs. When our ancestors still hunted for survival, wild wolves joined groups of humans and were used as scavengers. They were domesticated and artificially bred to become increasingly docile. Eventually, they were bred for selected traits such as size, hair length, color, and body shape. Over time, the genetics of these wolf descendants were altered so much that they hardly even resembled their ancient ancestors! This same process of selective breeding has been used on numerous animals ever since, including horses and cattle (Rangel, 2016).

In the past, artificial selection was not only used on animals, but also on various plants. The earliest archaeological evidence of our ancestors using artificial selection on plants dates back to 7800 BCE. This was first done in Asia on domestic varieties of wheat. It is through artificial selection that we have corn, which actually started out as a wild grass called teosinte and had tiny ears and very few kernels. Years of breeding for larger ears and more kernels created our current crop of corn. A similar process was also used to create broccoli with larger heads as well as sweeter apples (Rangel, 2016).

What the ancients accomplished still proves useful today, but, we have graduated to much more efficient and specific methods of altering the genes of living organisms. These developments have been relatively recent (most within the past 50 years) considering that modern humans have been around for approximately 200,000 years. The field of genetic engineering is still constantly changing, however, and advancements are being made almost daily.

The first huge breakthrough in genetic modification occurred in 1973 in the lab of Herbert Boyer and Stanley Cohen. These two scientists effectively cut out a gene from of one bacteria and insert it into the genome of another. They then used the recent discovery of an enzyme that cleaves the circular DNA plasmid of a bacteria at a single site. Within the gap this cleavage created, they inserted the gene of another bacterium that they knew would make it resistant to an antibiotic. After repairing the plasmid, the bacterium was allowed to multiply, and the subsequent bacteria contained the resistance to the antibiotic. Essentially, they took the antibiotic resistance from one bacteria and gave it to another that did not originally possess this resistance. Their experiments were one of the first demonstrations of the potential impact

of DNA recombination in the fields of medicine, pharmacology, and agriculture (Culliton, n.d). It only took one year for a similar procedure to be utilized in animals, specifically, mouse embryos.

Genetic modification has already had an enormous impact in the world of pharmacology. In 1982, the U.S. FDA approved the human use of genetically modified insulin. Insulin is a protein produced in the pancreas that helps regulate the glucose levels in our blood. People who have Type 1 Diabetes are not able to produce their own insulin and as a result, have unusually erratic glucose levels. Blood glucose levels must be regulated for the health and proper function of the body, but because they cannot produce their own insulin, Type 1 Diabetics must inject insulin to control their blood sugar levels. Through the genetic modification of yeast and bacteria, we have been able to mass produce a type of insulin very similar to our own.

The process used to produce insulin is very similar to the process they used in 1973 to grant antibiotic resistance to a bacterial cell. A plasmid, or piece of circular DNA, is extracted from either the bacteria or yeast cell. A small section is then cleaved, or cut, from the plasmid by restriction enzymes. The gene coding for human insulin is then inserted into the plasmid breach. This genetically modified plasmid is then introduced to a new bacteria or yeast cell and the cell starts dividing rapidly and produces insulin. The resulting insulin is then purified and packaged for consumer use.

Another area transformed by genetic engineering is the agricultural industry. The first field studies of genetically modified food crops utilizing recombinant DNA technology were

launched in 1987. Five years later, Calgene's Flavr Savr tomato became the first USDA (U.S. Department of Agriculture) approved food crop to be commercially produced. These tomatoes were genetically modified to increase firmness and have a longer shelf life. We should note that before this product was released to the general public, it underwent extensive health and environmental testing (Rangel, 2016).

Since the creation of the Flavr Savr tomato, we have found many other uses for genetic modification in agriculture. For example, we have been able to genetically modify food to make it more nutrient dense. In 2000, Golden Rice was developed with an increased vitamin A content to decrease fatalities linked to vitamin A deficiencies. Scientists have also made it easier for farmers to cultivate their crops through genetic modification. By developing plants that are resistant to herbicides, it has become easier for farmers to grow the crops they want and remove the unwanted ones.

Genetic modification has also facilitated advancements in medical research. The Caenorhabditis elegans, or round worm, has been instrumental in furthering the research of Alzheimer's disease. The round worm is very simple, with only approximately 300 cells in its entire nervous system, and nearly transparent. The transparency of the worm allows cells that have been tagged with green fluorescent protein to be seen through a microscope. This makes it possible to see the activity of various structures and proteins within the worm. The simplicity of the worm makes it easy to genetically modify to produce specific proteins that researchers want to study. In Alzheimer's studies, scientists genetically alter the genome of the worm to produce the APP gene, which is associated with Alzheimer's disease in humans. By essentially giving these worms Alzheimer's and studying the effects on its cells throughout its lifespan,

scientists have been able to further understand the role of these proteins in Alzheimer's disease ("What is genetic engineering?", 2017)

Where we are now

Like many things in science, genetic engineering has had to evolve over time to work out the kinks. Until very recently, altering the genetic code was very expensive, time consuming, and it lacked specificity. This all changed when the CRISPR-Cas9 system was discovered. CRISPR stands for "clustered regularly interspaced short palindromic repeats," and is a part of the genome of many bacteria that were initially puzzling to bacteriologists. They saw that many bacterial genomes had regions of unique genetic code, or "spacers," that were flanked by these short palindromic repeats. It was not until they compared the unique genetic sequences with known DNA libraries that they were able to begin to understand the reasoning behind these sequential patterns. In their comparisons, they discovered that a surprisingly large amount of these unique spacer sequences matched the DNA sequences of bacteriophages. They then realized that they were looking at the immune system of bacteria, used to defend against the bacteriophage (Chen, 2017). The CRISPR system provides immunity to bacterial cells by storing copies of pathogenic DNA into its own genome between palindromic repeats. This way, the next time the same pathogen tries to invade, the bacteria "remembers" the pathogen and can destroy the invader before it causes damage. This action is facilitated by an enzyme called CRISPR-associated protein 9 (Cas9) that scans the DNA pool, using guide RNAs (gRNAs), for any intruder that matches the existing unique sequences stored in the "databank." If it finds a match, Cas9 cleaves the DNA and signals the destruction of anything with that sequence.

This natural bacterial machinery has proven very useful in genome editing techniques. Scientists have found a way of manipulating the existing CRISPR-Cas9 system to make their own genetic customizations. This is done by creating a small piece of RNA with a short "guide" sequence that will bind to the specific DNA sequence the scientist is targeting. This guide RNA also binds to the Cas9 enzyme and leads it to the target DNA sequence. When it finds a match, just like in bacteria, the Cas9 enzyme cuts the targeted DNA. Once the DNA is cut, the DNA repair machinery of the cell is used to add or delete pieces of genetic material, or it makes changes to the DNA by replacing the cut segment with a customized DNA sequence.

The CRISPR-Cas9 system is currently the most specific gene editing technology available, yet, it is still subject to off-target sequence mutations. Researchers are currently working on ways to improve both the creation of guide RNAs and the Cas9 protein itself. Most of the research on genome editing is done using cells and animal models for the purpose of understanding human disease. Scientists are still working to determine whether the technology is safe for use on humans (Fu, 2014). Genome editing is the center of research on a wide variety of diseases, from single-gene disorders like cystic fibrosis, to more complex genetic diseases like cancer and HIV.

In the United States, gene therapy is currently available only as part of a clinical trial. It is also only approved for use on somatic cells, or cells other than sex cells. This means that edits made to the genome will not be passed on from generation to generation, and only affects certain tissues. The idea of this gene therapy is to replace the mutated, disease causing gene with a healthy one. This is commonly done using viruses as vectors to transport the

CRISPR-Cas9 components into the cells. This is a fairly effective method but there are certain risks associated with it.

The first major risk is the unwanted immune system response to the foreign "invader." The body has amazing ways of fighting off viral infections and for all it knows, this viral vector is a destructive pathogen. In some cases, the body will attack the virus carrying the healthy DNA, rendering it useless. The next notable risk associated with gene therapy is targeting the wrong cells. Viruses have the ability to infect a variety of cell types, which could be dangerous for the healthy cells of a patient. If the virus that was intended for cells with mutated genes infects a healthy cell, it could damage the healthy DNA, causing other illnesses or diseases. This leads to the next risk of current gene therapy methods which is that even if the virus infects the intended diseased cell, the healthy DNA could be inserted into the wrong spot in the genome and could lead to the formation of tumors (Gene Therapy, 2017).

The recent advancements in genome editing technologies have made it a very powerful tool with great potential for advancing science and treating human disease. However, there are still many risks associated with it that will require further investigation and advancements before it is considered safe for humans. This technology also raises many concerns, as it has the potential to modify the human germline.

The laws and regulations regarding the modification of human germline cells vary from country to country. As previously stated, the United States has only permitted the use of gene editing technology on somatic cells. Modifications made to the genes of egg or sperm cells (germline cells) or in the genes of an embryo could be passed to future generations.

Technically, we have the tools to make these modifications, but it is not yet fully understood or accurate enough to guarantee desirable results. While the consequences of somatic cell gene editing are limited to the cells of the patient only, this is not the case with genetic modifications made to germline cells. Unintended or long-term consequences of editing human germ cells and embryos have the potential to seriously affect not only the subjects themselves, but also their progeny. Because of the greater risks associated with germline gene editing, some countries, including the U.S., have enacted laws that restrict clinical use of human germline modifications. On the other hand, Chinese geneticists have already attempted to edit the genomes of human embryos.

Chinese researchers used the CRISPR-Cas9 editing technique to modify the gene responsible for β -thalassaemia, a potentially fatal blood disorder. The results of this experiment were both enlightening and cautionary. While the CRISPR-Cas9 gene editing technique has been well studied for adult somatic cells and animal embryos, this was the first published report of its use on human embryos. There had been many speculations about what would happen if this technique was used on human embryos, but this experiment provided actual data that can be used for further research. However, other than providing valuable data, this experiment was not considered a success. Not only did they find that hardly any of the surviving embryos contained the replacement genetic material, but also that the number of "off-target" mutations was much higher than in gene-editing studies of mouse embryos or human somatic cells. These findings further solidified the notion that this technology is still too immature for clinical use.

Advantages

The ability to edit our own genome comes with numerous exciting benefits. The enormous potential that the practice has to offer serves as a driving force behind the exhaustive research and advances in gene editing technology. If approached delicately and regulated diligently, human genome editing could affect countless lives for the better. This technology could wipe out disease, increase the quality and length of life, and even lead to a more advanced human race. With potential like this, it would be hard not to continue searching for answers.

The first, and probably most established, benefit of human genome modification is the ability to cure diseases. Not only could we treat existing diseases through advanced gene therapy, but we could completely remove diseases from future generations. How is that for preventative medicine? When we develop the technology and have a better understanding of the inner workings of the human genome, the world of medicine could be transformed.

In today's society, the main focus of medical resources is the treatment of existing disease. While preventative medicine is ideal, it is currently underfunded and not taken as seriously as treatment. For genetic diseases such as diabetes, there are certain measures that can be taken to lessen the likelihood of developing the disease. For example, the preventative measures for diabetes include a healthy diet and regular exercise. However, many people put little effort into prevention and eventually develop diabetes. There are also those who follow all of the guidelines for prevention and still develop the disease. From then on, their doctor visits

are focused on treating and controlling the disease, rather than preventing it. This person now has to check their blood sugar regularly, eat a strict diet, and receive insulin therapy for the rest of their lives. One could argue that since they had the genetic predisposition and still continued to live an unhealthy lifestyle, they brought it upon themselves. However, someone who did not have the genetic predisposition could theoretically live the same, or worse, lifestyle and never develop diabetes. They did not do anything to prevent the disease either, they just do not have the same genetic make-up that increased the risk for diabetes. It seems unfair and it is even less so for the person who followed all of the guidelines but still developed the disease. This situation would be a thing of the past with genetic modification. We could remove the genetic predisposition for diabetes before birth and even out the "playing field" we call life. This technology would give doctors the ability to truly prevent disease, rather than just treat it.

Human genome editing could be used to cure and prevent a number of terrible diseases including Alzheimer's Disease, Huntington's Disease, HIV, Sickle Cell Disease, Cancer, and many more. These diseases are not only a drain on individual lives and families, but on our society and economy as well. Many genetic diseases are debilitating and leave those they inflict unable to work or contribute to society. Those who cannot work because of their disability then have to turn to the government for financial support. The continued support of such a large population is a drain on the economy and its resources. In order to pay for disability services, the government increases the financial burden of those who are able to work through higher taxes. If we could remove the debilitating diseases through genetic modification, all parties would benefit. A number of diseases that currently leave people disabled and unable to

contribute to society could be cured with genetic modification, allowing these people to live a more fulfilling life with purpose and opportunity.

Among the many advantages of human genome editing is the potential to improve quality of life. Imagine that you are an expecting parent and you go into the doctor's office for a routine check-up. After running some blood tests, the doctor returns to your exam room with a look of concern. You know he has bad news and immediately start imagining the worst scenarios. Before your mind has too much time to wander, the doctor gently informs you that the fetal test results are indicative of down syndrome. All of a sudden your world comes crashing down around you. All of your dreams of your healthy baby growing up to be a doctor, astronaut, or President of the United States are replaced by shock and fear; fear that you will not be able to care for your own child's special needs, that she will be bullied at school for being different, that she will never be fully self-sufficient. All of these fears, and countless more, run through your head relentlessly. Your biggest fear of all, though, is that she will never get to live a normal, happy life. As a parent, you know that you are going to love this child with all of your heart, with down syndrome or without. However, you want the best life for your child and know that the road that lies ahead of a child with down syndrome presents many more challenges than that of a healthy baby.

Now, imagine the same scenario, but with the option of genetic modification. Immediately after informing you of your child's genetic disorder, the doctor begins going over your options for the future. You could choose to raise a child with down syndrome or you could have a procedure done to reverse the genetic mutation and have a healthy baby. Whether you

choose to go ahead with the procedure or not, the choice is yours. The option to choose genetic modification would allow parents to give their children a better, healthier start on life.

The most controversial advantage of human genome modification is the potential to genetically enhance the human race. While many people fear that this technology would be abused, with careful monitoring, it could be a very positive development for the betterment of humankind. Throughout history, humans have evolved and advanced not only survive, but to thrive. We have long been told that the thing separating us from other animals is our ability to use our imagination and intelligence to create tools and solve problems. When the problem was that we needed food, we created traps and tools for hunting and gathering. When we needed clean drinking water and feces-free streets, we created water filtration and sewage systems. When we needed to prevent the spread of disease and lower the death toll, we created vaccines that now avert between 2 to 3 million deaths every year worldwide. Our history is packed full of examples where we were faced with an obstacle that threatened our survival or way of life, and we overcame it by expanding our knowledge and advancing our technology. Could it be possible that genetic enhancement is simply the next step in our evolutionary journey?

Through genetic enhancement, we could give the next generation of humans the tools and abilities to continue progressing our race. Within the genome lies the code for our intelligence, physical characteristics, temperament, and strength. Many believe that genome editing is the key to unlocking our full potential. Others discourage such innovations for fear of the unknown consequences the alterations could have on the human gene pool. These fears are certainly warranted, and the current work being done with genome modification

technology makes the likelihood of eventually crossing this line very high. If proper guidelines and regulations are not put into place very soon, the fears surrounding the idea of a future with this technology are much more likely to become the reality.

Drawbacks

With any new practice or technology, nobody really knows the effects until it is tested. This, however, does not stop people from speculating and creating imaginary scenarios. There is plenty of proof of this speculative tendency stacked high on the shelves of libraries around the world. Many authors, film producers, and philosophers have made a living off of their active imaginations, writing of dystopian societies that revolve around genetically modified humans. While most of these works exaggerate for theatrical effect and increased profit, they are drawn from very real fears. They further instill the notion that if not handled properly, a technology as groundbreaking as altering the genetic makeup of human beings could have very scary and destructive consequences.

Since we have very little data specific to the negative effects of human genome modification on society, we have to put historical events into present context and from that, extrapolate a prediction for the future. While there have been countless predictions of possible drawbacks to human genome editing, I have narrowed it down to the top three most common, which include further social class division, enhanced military power, and evolutionary backlash. With potential drawbacks like these, a fear of gene editing technology is certainly warranted.

That human genome modification could create further division between the social classes is a very popular fear. As a society, we tend to look for qualities that make us different

and then use those qualities as a way of determining where we stand on the social hierarchical ladder. In the past, we have used religion, wealth, race, sex, and many more qualities to determine social standing. The fear is that soon we will have to add genetic modification to the long list of qualities to be judged.

Members of higher social classes are known to have more opportunities for improvement than members of the lower class. Upper class citizens can afford a higher education, which often leads to a higher income and increased social influence. As the rich become richer and the poor become poorer, the gap between the classes continues to expand. If genetic modification becomes an option for society, the fear is that only the rich will be able to afford it. This would result in the upper class not only being financially, intellectually, and socially superior to the lower class, but also genetically superior. Parents who could afford to genetically enhance their children would do so, and those who could not would essentially be dooming their child to a lifelong sentence of being a second class citizen.

One could ask how this is a significant difference from the current class system. Lower class parents already bring their children into the world at a disadvantage. Their children do not have all of the opportunities that upper class children do, and most children born into a lower class family remain in the lower class for the rest of their adult lives. The difference is, with the current class system, hard work and dedication can provide those born into the lower class with opportunities to eventually climb out. This certainly is not easy and is very rare, but it can be done. In fact, the people who had to work for their success usually end up using it better and

are more well-rounded individuals than those who had success handed to them. This, however, would not necessarily be the case when genetic enhancement is thrown into the mix.

Genetics play a key role in a person's physical, mental, and social abilities. If a person of the upper class is given superior genetics, it would be nearly impossible for a person of inferior class and genetic makeup to outcompete them. This would lead to a clear line drawn between those who have been genetically enhanced and those who have not. Children born into the world without genetic enhancements would forever be inferior to those who had genetic "gifts" bestowed upon them by their wealthy parents. While this situation has "Worst Case Scenario" written all over it, it is not completely out of the realm of possibility. If the technology is not controlled and fairly distributed, it could potentially have destructive effects on the social structure of society.

The next possible drawback of human genome modification technology is its potential to be abused and exploited for military and war purposes. There are plenty of nightmarish scenarios in support of this fear. These include, but are not limited to, the creation of a genetically superior military, advanced biological warfare, and involuntary genetic modifications. If left unregulated, other countries could use this technology as an unfair advantage in the event of a world war.

The final drawback of unregulated human genome editing is the fact that we simply do not know all of the long-term effects these changes will have on our species. Our genome has been altered over time through evolution and random mutations. In fact, evolution means that we are who we are now because of a series of random genetic mutations over a long period of

time. Those with "undesirable" mutations did not survive to reproduce, while those with mutations that made them fit for survival were able to reproduce and pass the mutations onto their progeny. This introduction of new mutations occurred generation after generation and eventually became the DNA that all humans share today, with only .1% variation from person to person. So, the genome of our species has taken a very long time to become what it is today through a very slow process of trial and error. We are now on the brink of a technological era where we can control our own genetic alterations, rather than leaving them to chance and random mutation. Not only can we control the alterations, but we can introduce them at an astonishingly rapid rates. Genetic modifications that took thousands of years of slow evolution can now be introduced into the genome in a single generation. As pioneers of this technology, we have no way of knowing the all the possible consequences this could have on the evolutionary progress of our species. Additionally, the consequences could take multiple generations to become apparent. Therefore, it is important to acknowledge the power of this revolutionary technology and tread lightly as we move forward in a controlled and patient manner.

Regulation

Presently, human genome modification is being heavily researched and it is an inevitable part of our future. This is both exciting and worrisome for the reasons previously discussed, as well as many more. This technology has great potential benefits, but if left unregulated, it could have devastating effects on our society and species. Now the question is, how do we go about regulating something that is currently so abstract and unpredictable?

A tool that could potentially change what it means to be human at the innermost basic level needs to be handled with care. If this technology were to be misused, there is no telling what consequences could be had on the human race. Additionally, these consequences would not be isolated to one specific region. Just as our entire race shares 99.9% of its genome, the consequences of changes made to the genome would be shared as well. Therefore, I believe it is important that the regulations governing this powerful tool be harmonized among all nations.

Currently, the laws governing genetic research and testing vary from country to country. While some countries have strict policies that prevent much progress from being made in the area, others have policies that are more lenient or non-existent. Many European countries legally prohibit any germline intervention. Other countries have advisory guidelines that are not strictly enforced. Still, there are many countries that simply have not considered the possibility of regulating the technology.

The United States uses a regulatory system that treats gene therapy as a biological drug or device. Therefore, it falls under the scope of the Food and Drug Administration (FDA) and is comprehensively regulated under laws regarding infection control, efficacy, and safety. In addition, the U.S. depends on advisory bodies such as the Recombinant DNA Advisory Committee to help make sure that the human clinical trials are run in accordance with the law. The U.S has a strong pre-market control system, but once products are on the market, the control greatly weakens. Physicians have the discretion to take a product that was approved for one purpose and use it for a different purpose, population, or dosage. This differs from the United Kingdom's system which has very strong post-market regulation of any procedures

involving embryos or human fertilization. Not only does it regulate the product, but it also determines where the product can be used and by whom.

The Japanese use an initial risk assessment to determine the regulation of drugs. They classify proposed drugs as high, medium, or low risk and regulate them accordingly. Once the initial determination of the level of risk for a proposed drug has been made, it is then treated with that degree of stringency throughout the regulation process. By contrast, in the United States, every drug is treated as equally dangerous from the beginning to the end. Every proposed drug is run through the same phases of testing for safety and efficacy. Japan has also recently added a conditional approval pathway that is specific to regenerative medicine and gene therapy products. This pathway allows promising medicinal products that are not yet fully understood to be put on the market on the condition that the product is further evaluated while on the market. There is concern that if new products from controversial fields such as embryonic stem cell research or gene therapy are put to use too early, any failure could set back the entire field. The challenge with the conditional approval pathway is finding a balance between quick progress and adequate risk assessment. Adverse outcomes will not only injure individuals, but could slow progress so much that individuals who could benefit in the future are denied the technology.

In Brazil, the laws regarding stem cell research, cell therapy, and genetically engineered foods have been updated by accretion. Basically, they are just adding new layers of laws on top of earlier, more general rules. The foundational laws are ones such as the constitutional prohibitions on the sale of any kind of human tissue and 1996 laws on the patenting of human

biological materials. As one could guess, this has caused widespread confusion and a halt on progress while people attempt to interpret how the laws are going to interact.

There are many problems that may arise when a technology as powerful as gene editing is not uniformly regulated. However, there are also numerous challenges that we would have to overcome to achieve internationally harmonized regulation. Nevertheless, the potential negative consequences of unregulated human gene modification far outweigh the potential obstacles in the path to such harmonization.

A compelling argument for creating consistent or uniform regulations of gene editing is to avoid "regulatory havens" that allow providers or consumers to circumvent procedural restrictions by travelling to jurisdictions with more lenient or non-existent regulations (Charo, 2016). This could potentially encourage other nations to under-regulate in order to profit from medical tourism. Harmonized standards could also reduce administrative costs in adopting and administering national laws. Additionally, global regulation could increase opportunities to share regulatory resources and workload. Finally, consistent standards may even promote equal health protection for the citizens of all nations .

There are many challenges and obstacles presented by harmonization of regulation standards across all nations. The first challenge is the fact that nations have different historical, economic, social, and cultural systems and values, which would likely translate into different approaches to the regulation of a powerful technology such as human genome editing. It would be difficult to balance one nations prudence with another's lust for discovery. This also presents the practical challenge of more than 100 nations coming to an agreement on regulatory

requirements. The process of reaching a consensus would be laborious, resource-intensive, and may not even be successful in the end (Human Genome Editing, 2017). Challenges aside, a technology powerful enough to deeply effect every nation, is a technology that every nation should have a hand in regulating.

With great power, comes great responsibility and it is our responsibility to do everything possible to preserve our race and ensure its survival. Human history is packed with countless technological advancements that increased our survival rates and improved our way of life. Human genome editing is an enormously powerful technology that could be the next step in our evolution. Due to the transformative health benefits offered by human gene modification, extensive research and development of the technology is already underway. I believe that the best way to reap the benefits of human gene editing without facing devastating consequences is through the world wide harmonization of regulation standards. Achieving cooperation and coordination of all nations will certainly bring about challenges, but if overcoming these challenges means the survival and prosperity of our race, the extra effort will be well worth it.

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